

# Multi-Layer Free Energy Perturbation

Ying-Chih Chiang and Frank Otto

*Department of Physics, Chinese University of Hong Kong, Shatin, N.T., Hong Kong*

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## Abstract

Free energy perturbation (FEP) is frequently used to evaluate the free energy change of a biological process, e.g. the drug binding free energy or the ligand solvation free energy. Due to the sampling inefficiency, FEP is often employed together with computationally expensive enhanced sampling methods. Here we show that this sampling inefficiency, which stems from not accounting for the environmental reorganization, is an inherent property of the single-ensemble ansatz of FEP, and hence simply prolonging the MD simulation can hardly alleviate the problem. Instead, we propose a new, multi-ensemble ansatz – the multi-layer free energy perturbation (MLFEP), which allows environmental reorganization processes (relaxation) to occur automatically during the MD sampling. Our study paves the way toward a fast but accurate free energy calculation that can be employed in computer-aided drug design.

Accurately evaluating the free energy change of a ligand binding to its receptor has a very practical use in computational drug design, i.e. determining the relative binding free energies between two drug candidates for lead- optimization. One of the most frequently employed method for this purpose is the so-called free energy perturbation (FEP) method [1], which states that the free energy change between the final target state T and the initial reference state R can be evaluated via a single ensemble average, i.e.

$$e^{-\beta\Delta A} = \langle e^{-\beta u} \rangle_{\text{R}}, \quad (1)$$

where  $\Delta A$  denotes the free energy change

and  $\beta = 1/k_{\text{B}}T$ , with the Boltzmann factor denoted by  $k_{\text{B}}$  and temperature by  $T$ . The term  $u$  denotes the perturbation introduced to the initial reference state, and its value is given by the potential difference between the target state T and the reference state,  $u = U_{\text{T}} - U_{\text{R}}$ . Finally, the symbol  $\langle \cdots \rangle_{\text{R}}$  represents that the canonical ensemble average is performed over the reference state R. In other words, the sampling is performed using the Hamiltonian of the reference state. Similarly, one can also sample the target state T for calculating  $\Delta A$ , this leads to the so-called backward FEP calculation, i.e.  $e^{\beta\Delta A} = \langle e^{\beta u} \rangle_{\text{T}}$ . Although Eq. 1 is the-

oretically exact, numerically evaluating the ensemble average often suffers from a problem of the sampling inefficiency. While plenty of methods, e.g. stratification (multi-step FEP) [2, 3], confine-and-release method [4–6], or replica-exchange molecular dynamics (with solute tempering) [7–12], have been developed to improve the sampling efficiency and hence advance the FEP convergence, the current computational cost of using enhanced sampling methods combined with FEP is still rather prohibitive to be regularly applied in drug design [13, 14]. Hence, further pursuing an accurate but fast free energy method is still desirable.

Previously we have shown that the insufficient sampling comes from missing the environmental reorganization [15], e.g. allowing the water to move or reorient to accommodate the inserted ligand (perturbation). This process is a type of *relaxation process*, which is well studied in gas phase reactions. For instance, consider the quantum nuclear dynamics [16–18] during the interatomic/intermolecular Coulombic decay process (ICD) [19–24], in the neon dimer [17, 25]. After introducing a strong perturbation to the system (ionizing an inner valence electron on Ne), the system quickly responds to this perturbation by emitting one electron on the neighboring Ne, resulting in a  $\text{Ne}^+\text{-Ne}^+$  state that undergoes Coulomb explosion to

lower the system (free) energy. Clearly, the nuclear motion in the electronic decay process is always governed by the corresponding Hamiltonian of a specific electronic state [16]. Similarly, in the classical molecular dynamics, the molecular motion is also governed by the Hamiltonian of the simulated system. The only difference is that the classical system is described by Newtonian mechanics [26] with force fields [27].

Let us now consider a common illustrative example in free energy calculations, namely, the ligand solvation process. According to Eq. 1, collecting the ensemble governed by the Hamiltonian of reference state R (ligand and water solvent are separated) is sufficient for correctly evaluating  $\Delta A$ . However, as illustrated in Fig. 1, the two end states can have very different potential energy landscapes so that their associated probability distributions center at different geometries, as indicated by the dotted curves in Fig. 1. Consequently, when sampling the distribution via MD simulation in order to sample all possible conformations of the reference state R, one faces the sampling inefficiency because the relevant microstates belonging to the target state T are generally missed, leading to a non-converged free energy result. This problem can be solved by introducing the reorganization process (relaxation) into the sampling procedure by start-

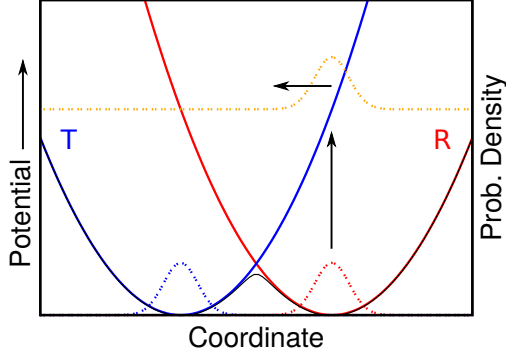


FIG. 1: Local potential trap and the insufficient sampling problem. The reference state R and the target state T have their own potential landscapes (solid curves) that confine the sampled probability distributions (dotted curves). When any conformation that belongs to the distribution of R is placed on the landscape of T, it will move according to the Hamiltonian of T, leading to the reorganization process.

ing at the same conformation as reference state R but performing the MD simulation based on the Hamiltonian of target state T, see e.g. the orange dotted curve in Fig. 1. While this idea may not be so familiar to the native biophysics society, its quantum version is regularly performed in studying gas phase molecular dynamics involving multiple electronic states [16–18, 28, 29]. Furthermore, our approach is very different from contemporary enhanced sampling schemes, e.g. increasing temperature to overcome the potential barrier, adding a biasing potential to flatten the potential landscape, or even using the “adiabatic” potential (black curve) for sampling [30]. These schemes focus on forcing the MD sampling to explore a larger confor-

mational space but continue using Eq. 1 to evaluate  $\Delta A$ . Rather, we believe that the insufficient sampling problem is an inherent property such that the best way to solve it is to use a different working equation than Eq. 1.

Does such a new equation, which allows the system to relax automatically during the simulation, exist? Exploiting the fact that  $e^{-\beta\Delta A}$  is a constant under the given NVT ensemble, further imposing one additional sampling over a normalized distribution will not change its value, e.g.  $\langle e^{-\beta\Delta A} \rangle_T = e^{-\beta\Delta A}$ , as long as the sampling is sufficient. Hence we have,

$$e^{-\beta\Delta A} = \langle \langle e^{-\beta u} \rangle_R \rangle_T, \quad (2)$$

where the definitions of all symbols are identical with Eq. 1. In Eq. 2, we further imposed the sampling over the distribution of target state T, which does not affect  $\Delta A$ , since its value is already determined at the sampling of the reference state R. While Eq. 2 seems to introduce more effort in MD sampling to evaluate  $\Delta A$ , this equation actually allows the environmental reorganization. Let us explain. When evaluating Eq. 2, one first performs a short equilibrium sampling to collect the microstates that belongs to state T, and then from each microstate (each frame of the collected trajectory) one performs an

MD sampling using the Hamiltonian of state R to evaluate the free energy change within this simulation. Thus, each microstate of state T gives one  $e^{-\beta\Delta A}$  that will later participate in the ensemble average over state T. Interestingly, for each microstate, the sampling now always begins at a non-equilibrium high energy conformation. This conformation will then undergo a relaxation process automatically due to the governing Hamiltonian, and hence the sampling is more efficient than waiting for rare events to happen. For practical purposes, Eq. 2 can also be expressed in a reversed sampling form that reads,

$$e^{\beta\Delta A} = \langle e^{\beta\Delta A} \rangle_R = \langle \langle e^{\beta u} \rangle_T \rangle_R. \quad (3)$$

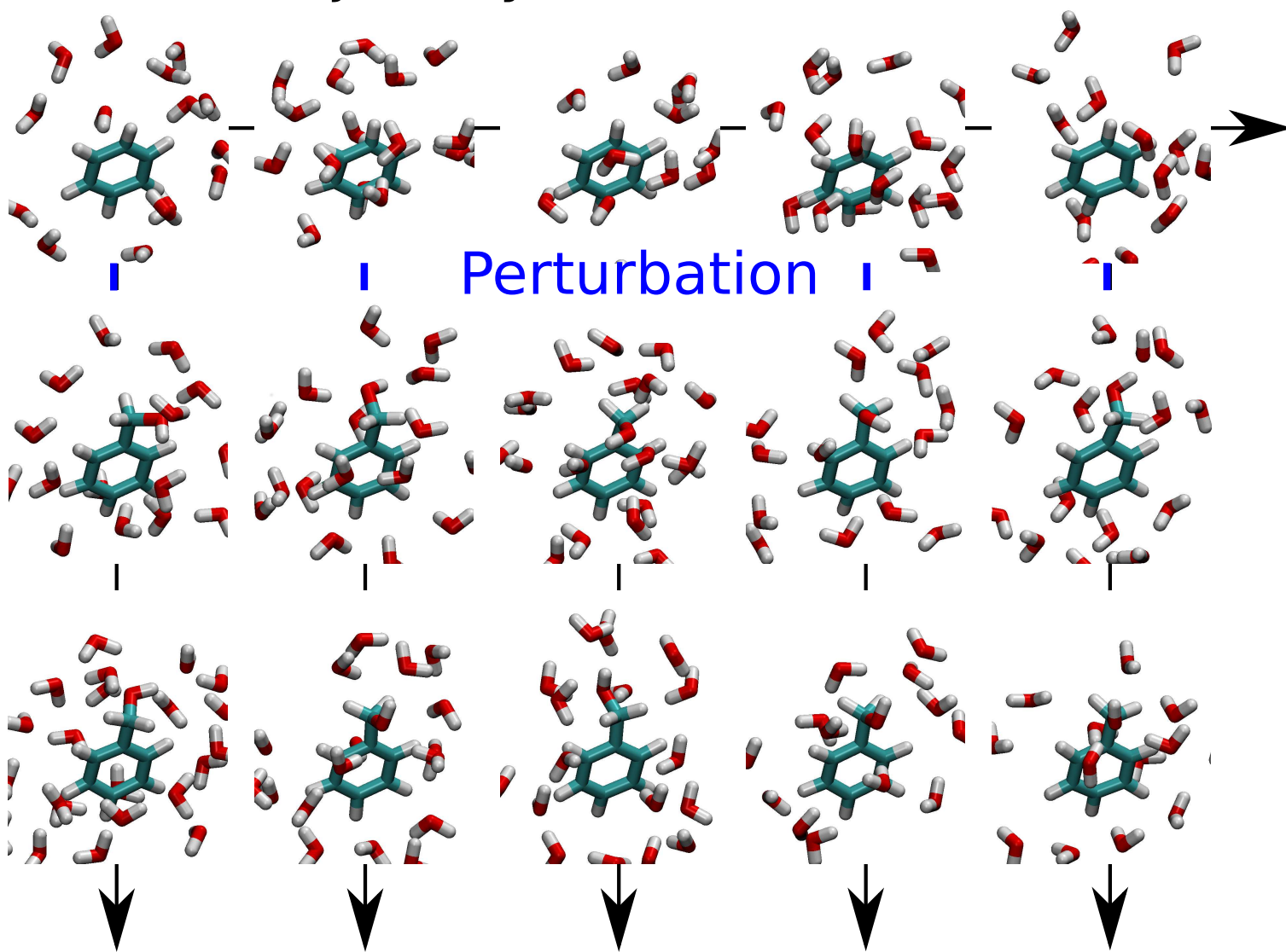
This new format describes the process in Fig. 1: start the sampling under the reference state R, and then introduce the environmental reorganization via the relaxation process governed by the target state T. One additional advantage of Eq. 3 is that we can now assign a common reference state R and save the trajectory for evaluating  $\Delta A$  between the reference state and different target states. This can further save some computational effort. Finally, since Eqs. 2-3 already go beyond the usual FEP theory, we will term our new approach as the multi-layer free energy perturbation (MLFEP), in order

to distinguish it from the virtual substitution scan (VSS) [15, 31] which is purely based on a single-ensemble approach but also has a dual sampling format.

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MD trajectory of the reference state



Short MD simulations